



## REVIEW ARTICLE

# Insect repellents and associated personal protection for a reduction in human disease

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**Abstract.** Personal protection measures against biting arthropods include topical insect repellents, area repellents, insecticide-treated bednets and treated clothing. The literature on the effectiveness of personal protection products against arthropods is mainly limited to studies of prevention of bites, rather than prevention of disease. Tungiasis was successfully controlled by application of topical repellents and scrub typhus was reduced through the use of treated clothing. Successful reduction of leishmaniasis was achieved through the use of topical repellents, treated bednets and treated clothing in individual studies. Malaria has been reduced by the use of insecticide-treated bednets (ITN), certain campaigns involving topical repellents, and the combination of treated bednets and topical repellents. Although area repellents such as mosquito coils are used extensively, their ability to protect humans from vector-transmitted pathogens has not been proven. Taken together, the literature indicates that personal protection measures must be used correctly to be effective. A study that showed successful control of malaria by combining treated bednets and topical repellents suggests that combinations of personal protection measures are likely to be more effective than single methods. Implementation of successful programmes based on personal protection will require a level of cooperation commonly associated with other basic societal functions, such as education and food safety.

**Key words.** Individual prevention, insecticide-treated bednet, integrated pest management, malaria, mosquito, mosquito coil, public health, repellent, vector-borne disease.

## Introduction

Repellents continue to be widely available in a variety of forms. One previous study estimated that total sales of topical repellents in the U.S. is \$200 million per year and growing (Black, 2003), motivated by West Nile virus and Lyme disease. The U.S. Environmental Protection Agency (EPA) lists 684 registered topical repellent products on their repellent data set, which is part of a laudable attempt to inform the consumer about protection times from mosquitoes and ticks (U.S. EPA, 2011). The reasons for the popularity of insect repellents are difficult to quantify, although there have been open-source studies of opinions (Frances & Debboun, 2007) and many proprietary marketing studies by major manufacturers.

Common sense and experience with the public suggest that the perceived essential advantage of repellents is that they can be easily used by the individual, imparting a sense of control over exposure to biting arthropods. In the present study, we attempt to review the relevant literature that provides evidence, either direct or circumstantial, that repellents can contribute towards disease prevention. The evidence is not quantified in a meta-analysis, but considered in a simple logic of the most relevant studies.

For the purposes of this study, we would like to consider repellents defined broadly to include some of the products designed for use by an individual or small group to reduce the number of bites from hematophagous arthropods (White, 2007). Such products include topical repellents applied directly

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to the skin, but they also include compounds on clothing, insecticide-treated bednets (ITN) and various devices that emit vapour or droplets into a small space (e.g. mosquito coils) (Strickman *et al.*, 2009). Area repellents, ITNs and treated clothing often have insecticidal as well as repellent properties, but our review of the literature discussed below showed that combinations of these methods are more likely to protect individuals; therefore, a review of personal protective measures that are not strictly speaking repellents was necessary. The use of these products have a long history (Moore & Debboun, 2007), but it is only since 1942 that there has been a concerted effort to use repellents to prevent transmission of arthropod-borne pathogens. During that year, the Orlando Laboratory of the U.S. Department of Agriculture was funded by the National Emergency Council (as requested by the U.S. Army Surgeon General) to develop methods for protection of military personnel from epidemic typhus, scrub typhus, plague and malaria. The result was the development of many of the modern strategies for vector control that we take for granted now, including highly effective, synthetic repellents (Knippling, 1949; Joy, 1999).

Major government agencies have endorsed the use of repellents as an important part of an individual's protection from infection. The EPA currently has a web page (U.S. EPA, 2010) that helps people find an appropriate topical repellent. The introductory material includes the following statement:

Effective insect repellents can protect you from serious mosquito- and tick-borne diseases. In the United States, mosquitoes can transmit diseases like St. Louis encephalitis and West Nile virus. Ticks can transmit serious diseases like Lyme disease, Rocky Mountain spotted fever, and Ehrlichiosis.

The U.S. Centers for Disease Control and Prevention (CDC) made the positive statement that, 'Repellents are an important tool to assist people in protecting themselves from mosquito-borne diseases' (CDC, 2008). They specifically recommended topical repellents containing DEET (Frances, 2007a), Picaridin (Frances, 2007b), *p*-menthane-3,8-diol (PMD) (Strickman, 2007a), or IR3535 (Puccetti, 2007) and repellents for clothing that contain permethrin. The U.S. military promotes personal protection using treated clothing and topical repellents (as well as other personal protective measures) in a detailed manual (Armed Forces Pest Management Board, 2009), which states that chemical repellents can be the only means available to avoid bites and associated diseases under certain conditions.

The logic of disease prevention is that repellents reduce the number of arthropod bites and that arthropod bites are a necessary step in the transmission of vector-borne pathogens; therefore repellents reduce the occurrence of infection and disease. This simple syllogism is not nearly as obvious as it sounds, principally because only one inoculative bite is required for infection and in some situations multiple inoculative bites would be received over a short period of time. Under those circumstances, stopping a proportion of bites might have no effect on the incidence of disease as enough vectors overcome the repellent to increase the chances of getting infected over

a short period of time. This study reviews the literature on the prevention of disease in individuals by repellents, including repellents on the skin, in clothing and dispersed in the air. We did not consider possible population level effects, such as selection of vector populations that do not tend to feed on humans or direction of vector populations to lethal treatments ('push-pull' strategy). We conclude that on a practical level, repellents can reduce the incidence of disease caused by vector-borne pathogens but they can only rarely eliminate the risk because of the imperfections of use by individuals.

### *Integrated disease control and the range of repellent products*

Integration of disease control is seen by some as an essential move towards effective management of tropical diseases (Grépin & Reich, 2008). The basic idea of integration applied to disease control is that linkages between those programmes that exist can make actual health delivery as good as possible within the local context. Entomological interventions and other activities usually grouped as environmental health are often organized by entities outside of the more usual veterinary and public health communities; therefore, the integration of entomological interventions into health delivery is likely to require a special effort. A fair question asked by human health practitioners is whether entomological interventions actually reduce disease incidence, rather than just relieve the annoyance of arthropod bites. Presumably, good evidence for the effectiveness of repellents in reducing the incidence of infections by vector-borne pathogens resulting in disease would allow public health strategists to integrate repellent use into their programmes. The concept of integrated pest management is more familiar to entomologists and its commonly designated components of risk assessment, surveillance, control and sustainability (Strickman, 2008) could certainly be applied to integrated disease control. In the context of integrated disease control, this would mean defining the disease to be controlled, determining where its aetiological agent is transmitted, assembling the right tools for both medical and entomological intervention, and designing a programme that can achieve its goals permanently by constant response to the real and current situation.

There is a wide range of repellent products available for consideration in an integrated disease control programme. Topical repellents are applied as a spray, lotion or cream directly on exposed skin. The inherent efficacy of each product depends on its active ingredients and its formulation. The usual standard is for complete protection from the target arthropod, so that relative effectiveness is judged by duration of protection (Barnard *et al.*, 2007). In fact, this standard is unrealistic and thorough tests in the field often indicate that protection is high (greater than 95%) but not perfect even shortly after application. On the other hand, the protective effect does not cease suddenly and there is partial protection for some period after biting becomes noticeable (Barnard & Xue, 2007). Area repellents (Strickman, 2007b) are products that disperse a chemical into the air, repelling or killing flying, biting arthropods from the immediate vicinity. The most common area repellents are coils that burn a flammable matrix to release gaseous and finely particulate active ingredient into the air. The repellent action of coils is

presumed to last as long as the coil is burning but as protection is seldom near 100%, the percentage of bites is the usual measure of effectiveness. Other area repellent products are not nearly as common as coils, but they either actively disseminate a chemical through heating (e.g. electrically heated mats or liquids for indoor use) or air currents. The active ingredients of most area repellent products are pyrethroids that kill some insects and repel others. Repellents can also be applied to clothing (McCain & Leach, 2007). There is a long history of the use of various chemicals, the current standard being permethrin applied as a spray, dip, soak or integrated into the textile during manufacture. Treated clothing stops bites through the cloth or deters chiggers and ticks from attaching; the clothing does not affect bites on adjacent exposed skin and not every insect that contacts the clothing is killed. Finally, ITNs are a popular tool for malaria control, especially in sub-Saharan Africa (Lengeler, 2009). Current systems either depend on soaking the nets in insecticidal solution or integrating insecticide into the nets at the time of manufacture. In anti-malaria programmes, ITNs are advocated as a relatively inexpensive and long-lasting method to protect people from night-biting vectors of the *Plasmodium* pathogens. There is also evidence that ITNs can be helpful in preventing transmission of leishmaniasis (Elnaiem, 2011) and Chagas disease (Kroeger *et al.*, 2003).

The expectation that repellents will reduce the incidence of disease caused by vector-borne pathogens is repeated often in the literature. Gupta & Rutledge (1994) summarized repellent systems and their history, stating that repellents are a cheap and practical way to prevent bites and disease. They gave examples that represented well-documented disease reduction achieved with repellent clothing (scrub typhus; McCulloch, 1946) and topical repellents (sand fly fever; Philip *et al.*, 1944). They also described studies that were less well controlled in which the use of local preparations for cosmetics or emollients were associated with reductions in malaria. More recently, Goodyer *et al.* (2010) performed an extensive review of comparative efficacy, concluding that the topical active ingredients DEET, Picaridin and PMD, as well as treated clothing and ITNs, offered the best potential protection from malaria. They concluded that IR3535 was a less effective topical repellent and that citronella, neem, essential oils and area repellent systems are inadequate to significantly reduce the risk of disease.

Another expression of the expectation of disease protection is in reviews of operational or experimental repellent use. Cope *et al.* (1996) suggested that the low incidence of leishmaniasis (31 cases) and sand fly fever (no cases) among 697 000 American military personnel participating in Operation Desert Storm in Saudi Arabia, Iraq, and Kuwait from December 1990 to May 1991, was as a result of the use of insecticides, repellents and other protective measures. The authors stated that the incidence of the two diseases might have been higher during warmer parts of the year and Killick-Kendrick & Peters (1992) thought that weather rather than repellents were responsible. There are many other examples of testing protection from bites with the implication that reduction in the number of bites will lead to less disease. Two studies in Ghaziabad, Uttar Pradesh, India (Ansari *et al.*, 1990; Mittal *et al.*, 2011) measured the efficacy of repellents against

*Anopheles culicifacies* (Diptera: Culicidae) Giles, *annularis* Van der Wulp and *subpictus* Grassi. They found that DEET-based repellents prevented 93–100% of bites during 11 h at night, by contrast with indoor use of mosquito coils that provided only about 76% protection.

A more critical attempt to relate bite protection to disease protection has been made by Kiszewski & Darling (2010). They proposed that the following equation could be used to make a quantitative estimate of *Plasmodium* (Haemospororida: Plasmodiidae) Marchiafava & Celli transmission from measurements of repellent efficacy:

$$F_e = (1 - sh)^{b(1-rc)}$$

where

- $F_e$  = the probability that a person avoids malaria during the given time period
- $s$  = sporozoite rate in mosquitoes
- $h$  = the proportion of infective bites that cause disease
- $b$  = bites per person per time period
- $r$  = proportion of bites avoided by wearing repellent
- $c$  = proportion of people who use the repellent (product acceptance).

A hypothetical application of this model showed that a repellent that prevents 98% of bites and is used by 98% of the population will reduce the cases of malaria by 88.9% during a 7-month transmission season in which 1.5% of mosquitoes are infected and a person receives an average of 40 bites per night. The calculated reduction in disease becomes much less as efficiency of protection ( $r \times c$  in the equation) decreases or as the number of bites per day increases. For example, the decrease in malaria incidence during 7 months is only 48.2% if the repellent prevents 95% of bites and 80% of people use the product. An unpublished report by Del Cielo (Appawu *et al.*, 2011), a private enterprise promoting the use of repellent for malaria prevention in the poorest communities, used data from Kassena Nankana District, Ghana to calculate the reduction in disease from actual use experience. In that community they observed a biting rate of 86 *Anopheles gambiae* (Diptera: Culicidae) Giles and *funestus* Giles bites per person per night and 1% of those mosquitoes infected (entomological inoculation rate of 418 infective bites per person per year). Distribution of 'NO MAS,' Del Cielo's repellent containing PMD and lemongrass oil in a water-based formulation, resulted in its use by 97% of the people and investigators measured 90% protection from bites. Using Kiszewski and Darling's equation, an untreated population in the same area would have had 1.87% of its inhabitants infected with malaria per night compared with only 0.25% infected if they used NO MAS. This would reduce the number of cases by 75.8% during 3 months at a cost of US\$0.033 per person per day.

#### Repellent field trials and disease reduction

There have been relatively few studies that measured disease as an outcome after the use of repellents. The lack of studies probably has many causes. First, the common

sense assumptions of efficacy outlined above may reduce the motivation to invest in those studies, leading to the practice of distributing repellents for disease control based on hope rather than evidence. Second, repellents are not considered to be medical items and have been regulated based mainly on safety rather than efficacy. Finally, the standards for clinical studies based on the principles of informed human consent, good laboratory practice, double-blind design (in which neither the investigators nor subjects can detect whether a placebo or treatment is administered) and sufficient sample size to achieve significant statistical power, are considered extremely costly compared with the potential financial market for the products. Nonetheless, there appears to be more interest in performing repellent trials that measure disease as the principal outcome. This interest is in response to the admirable increase in effort to establish better programmes for control of diseases caused by vector-borne pathogens.

Non-infectious diseases for which the arthropod is the direct cause of pathology are often not considered to be of major public health significance, but these conditions can be extremely important in communities where they are common. Although not technically considered vectors, these insects can impair the health of a community as surely as an infectious disease. One example is pediculosis, the infestation of people with lice (Burgess, 1993). An effective repellent applied after treatment would be useful to prevent the reinfestation as individuals were sequentially treated. Another example is the chigoe flea, *Tunga penetrans* (Siphonaptera: Hectopsyllidae) (Linnaeus), infestations of which can incapacitate people. Schwalfenberg *et al.* (2004) and Feldmeier *et al.* (2006) reported careful trials in Fortaleza, Brazil using a cosmetic product with repellent properties to nearly eliminate (92% reduction) infestations that had affected half the community. Two of the early successes using repellents to reduce infectious disease involved sand fly fever and scrub typhus. In a previous paper that is one of the classics of medical entomology, Cornelius Philip teamed up with two scientists who went on to great fame in the battle against polio, John R. Paul and Albert B. Sabin (Philip *et al.*, 1944). They identified sand fly fever transmitted by sandflies as a key problem for the U.S. military stationed in Cairo during World War II because each case involved 6–10 days off duty. In 1943, they reported that 25% of the troops were infected. In a controlled trial from 24 September to 30 October 1943 they showed that 2 out of 57 (3.5%) non-immune volunteers treated with repellent were infected compared with 12 out of 83 (14.5%) untreated volunteers, resulting in a 76% reduction in disease. They used military issue dimethyl phthalate on exposed skin, applied just before going to bed.

Scrub typhus, caused by *Orientia tsutsugamushi* (Rickettsiales: Rickettsiaceae) (Hayashi) and transmitted by chiggers in the genus *Leptotrombidium* (Trombidiformes: Trombiculidae) Nagayo, remains an important rickettsial disease in Asia and Australasia, although the advent of modern antibiotics has greatly reduced mortality (Smadel *et al.*, 1948; Kelly *et al.*, 2002). Effective clothing repellents were developed by the U.S. Department of Agriculture (Madden *et al.*, 1944), largely solving the problem for the U.S. military during World War II and establishing a precedent for the treatment of uniforms with

repellents that continues today (Brown *et al.*, 2005). Field tests with dibutyl phthalate applied every 2 weeks to uniforms of Australian soldiers resulted in a 90% decrease in scrub typhus (McCulloch, 1946). Welt (1947) performed a controlled trial with American soldiers from August to November 1944. One battalion (approximately 600 people) did not receive treatment, the uniforms of another battalion were sprayed with dimethyl phthalate and the uniforms of 2.5 battalions (approximately 1500 people) were treated with an emulsion formulation of dimethyl phthalate. All of the soldiers then performed combat operations for 7–10 days in areas with scrub typhus transmission. The dimethyl phthalate spray reduced the number of cases by 64% (from 45 cases in the control group to 16 cases in the sprayed group) and the emulsion reduced the number of cases by 94% (to 7 cases).

Most repellent trials that measured a reduction in disease were directed at malaria. Some studies have failed to show any significant effect on transmission, in spite of thorough sampling and analysis. Schoepke *et al.* (1998) collected survey data from European tourists returning from East Africa, analysing the responses of 89 617 people. They found that 1.8% of them (1594 people) reported using all possible preventive measures, including sleeping in air conditioned rooms and taking chemoprophylactic drugs. Surprisingly, these thorough measures only reduced malaria incidence by 50% compared with people who took no precautionary measures at all (4.8%, 4319 people). Corrected for chemoprophylaxis, the analysis showed that only sleeping in an air conditioned room and wearing long sleeves and trousers were significantly related to a lower malaria risk; bednets, aerosol insecticide spray, topical repellents, vitamin B, mosquito coils and electric fumigators made no difference. Local residents ( $n = 547$ ) in the Chennai (Madras) region of India who sought diagnosis in a malaria clinic were questioned about their use of repellent measures, dividing the respondents into those with malaria and those without malaria (Srinivas *et al.*, 2005). The only significant risks were failure to close windows and doors at night [odds ratio (OR) 1.61 after adjustment for other factors] and having at least one member of the family with a history of malaria (OR 1.64). Of all the patients, 7% with malaria used topical repellents, 13% used insecticidal mats and 43% used mosquito coils, compared with 2%, 14% and 44% without malaria, respectively.

Treated clothing provided significant protection from malaria and leishmaniasis during a study conducted in Colombia (Soto *et al.*, 1995). Soldiers who wore permethrin-treated uniforms 24 h per day for 4.2 weeks had 75% less malaria (3 cases out of 86 soldiers) than a group with untreated uniforms (12 cases out of 86 soldiers). The soldiers with treated uniforms exposed in an area with infected sand flies for 6.6 weeks had 83% less leishmaniasis (4 cases out of 143 soldiers) compared with soldiers with untreated uniforms (18 cases out of 143 soldiers). By contrast, Thai soldiers in a highly endemic area of Sisaket Province were not protected from malaria by wearing permethrin-treated uniforms (Eamsila *et al.*, 1994). During October through to April 1992, 44.5% of 137 soldiers with treated uniforms got malaria compared with 39.5% ( $n = 266$ ) in the placebo group. These soldiers were not given any instruction to wear their uniforms at night and they were not



given topical repellents. In a modification of treated clothing, Rowland *et al.* (1999) issued permethrin-treated headscarves to Afghan women ( $n = 395$ ) in a Pakistani refugee camp. The headscarves were typically used by men, women and children as a top sheet while sleeping. When malaria incidence was 14.8% per year, they observed a 64% reduction among children up to 10 years old and a 38% reduction among people less than 20 years old, but no reduction among people more than 20 years old.

There is a great deal of literature on the effectiveness of ITNs, summarized in a meta-analysis by Lengeler (2009). Five trials with childhood mortality as an endpoint showed 17% protection compared with no net and 23% protection compared with an untreated net. Overall, the use of ITNs would save 5.5 children's lives per year per thousand children. Another 21 studies indicated that ITNs reduce the incidence of malaria in areas of stable *Plasmodium falciparum* (Haemospororida: Plasmodiidae) Welch transmission by 50% and in areas of unstable transmission by 62%. *Plasmodium vivax* (Haemospororida: Plasmodiidae) Grassi & Feletti transmission was reduced by 52%. In Africa, the challenge for ITNs is considered to be effectiveness rather than efficacy, in that the impact of ITNs is influenced by the use patterns of individuals (Lengeler & Snow, 1996). ITNs were also useful in Latin America. A trial in Chinandega, Nicaragua showed that in households where 31–70% of people used ITNs, the homes had 68% less malaria (Kroeger *et al.*, 1999). A 35-week Thai study (Kamol-Ratanakul & Prasittisuk, 1992) showed less effectiveness in Chonburi, where those who slept under ITNs ( $n = 126$ ) were only 6% less likely to get malaria than those who slept under untreated nets ( $n = 135$ ).

Topical repellents' effect on malaria transmission has been studied in various ways and with a number of unusual products. Pregnant Karen tribeswomen ( $n = 897$ ) near the Thai-Burmese border participated in a 17-month trial (McGready *et al.*, 2001) of traditional *thanaka* cosmetic [extract of *Limonia acidissima* (Sapindales: Rutaceae) L.] compared with *thanaka* mixed with 20% dimethylbenzamide (an analogue of DEET). Although the incidence among women with the repellent cosmetic was lower (10.6% incidence of *P. falciparum*; 21.1% incidence of *P. vivax*) than among the women with normal cosmetic (14.8% *P. falciparum*, 26.4% *P. vivax*), the difference was not statistically significant. A repellent soap from Australia containing 20% DEET and 0.5% permethrin has been used in Ecuador and Peru (Kroeger *et al.*, 1997) and Pakistan (Rowland *et al.*, 2004a). Properly applied, the soap is put on as a normal wet solution, but it is not rinsed off. In Ecuador, a village with the soap started with a malaria prevalence of 12.8% and completed the study with a prevalence of 8.5%, which was no difference from a village without the soap (starting at 14% prevalence and ending at 6.7%). The Peruvian village with soap had 25% less malaria (prevalence starting at 13.9% and ending at 17.9%) than the village without soap (starting at 12.6% and ending at 24.1%), but the difference was not significant. The trial in Pakistan involved 25% of an Afghan refugee village (population 3945) in Northwest Frontier Province. During 6 months, the people using the soap had an incidence of 3.7% *P. falciparum* (23 cases among 618 people) compared with 8.9% (47 cases

among 530 people) in the placebo group, indicating a statistically significant 56% reduction. By contrast, *P. vivax* cases were not reduced in the treated group, possibly because of relapses from infections acquired before the study. A study was performed in a similar community (Rowland *et al.*, 2004b) in which the soap was offered for sale and residents surveyed on whether or not they used the soap and ITNs. Use of the soap was associated with a 45% decrease in malaria, ITN use was associated with a 46% decrease and use of both the soap and ITNs was associated with a 69% decrease ( $n = 709$ ). Only 43% of the households purchased the soap and only 7.8% recalled using it within the previous 10 days, suggesting that user acceptance of the soap was not high but that those with greater risk of transmission used the soap more frequently.

More conventional topical repellents were used successfully against malaria in South Africa. Durrheim & Govere (2002) provided a product with 15% DEET to the community of Albertsnek, South Africa (population 850) during 21 weeks in 2000. The interiors of residences had been sprayed with deltamethrin the previous December, but flooding had wetted walls and compromised the effectiveness of the insecticide. Residents were instructed to apply the repellent to their ankles and feet at sunset and again just before going to sleep. The application was limited to the part of the body most commonly bitten by *Anopheles arabiensis* (Diptera: Culicidae) Patton, the principal vector of the area. This procedure reduced malaria cases from 42 per week at the beginning of treatment to an average of 16 cases per week during the final 8 weeks.

The most thorough trial of the efficacy of repellents for a reduction in malaria was funded recently by the Bill and Melinda Gates Foundation in Beni, Bolivia (Hill *et al.*, 2007). This careful study followed standard procedures for clinical trials, being double-blind and placebo-controlled. It involved 4008 volunteers in 860 homes for a total of 15 174 person-months of risk examined. All used ITNs and half (2041 people, 436 homes) used 10 mL of 30% PMD applied to the legs, arms and neck between dusk and bed time. The repellent group had an 80% reduction in *P. vivax* malaria and an 82% reduction in *P. falciparum* malaria (although not statistically significant because of the small number of cases). The use of the repellent from after dusk combined with ITNs resulted in an overall reduction of fever by 58%. The authors concluded that use of repellents combined with ITNs could protect local populations, as well as travellers, from malaria.

#### Practical considerations and future developments

A review of the literature on the use of topical repellents, ITNs, and area repellent devices has implications for research needs and, more importantly, for effective use of these important tools. In many ways, evaluation of ITNs is at a mature stage where further studies can be focused on local conditions, new combinations of methods or new kinds of ITNs, rather than on proof of the concept. This sort of research may be necessary in spite of the extensive testing done to date, exactly as considerable effort is expended to test marketed products for refinement of their application, integration with other methods

and to monitor effectiveness. ITNs clearly reduce the incidence of malaria in many situations, but they have never been shown to eliminate all transmission. The implication is also clear that they would provide a level of protection from other pathogens transmitted by flying insects that bite at times when a person is under the bed net. Future studies and product development will probably further improve efficacy by selection of alternative chemicals for resistance management (Pennetier *et al.*, 2005, 2007) and adjustment of the many economic and cultural factors that influence actual use by the individual (Kroeger *et al.*, 2002). The indication that an additional reduction in malaria can be achieved by combining ITNs with topical repellents points to the continuing need for studies on the integration of methods. In spite of the strong evidence provided by individual studies, the quantitative relationship between protection provided by ITNs and topical repellents can only be calculated based on assumptions of biting rate and transmission. Many more studies with disease as an endpoint would be necessary to understand the use of these two tools to the point that there would be reliable predictions of effectiveness.

Although treated clothing is widely used by the military, its actual effectiveness in preventing malaria and other diseases caused by pathogens transmitted by flying insects appears to be highly dependent on its use. The inherent problem is that people do not generally sleep in their clothes and important vectors bite at night. Another problem is that treated clothing does not protect the individual from bites on exposed skin. In the authors' opinion, additional development of clothing products that improve textiles as mechanical barriers, alternatives to pyrethroid active ingredients and the use of volatile components that protect adjacent exposed skin would be welcome improvements. By contrast, treated military uniforms appear to be highly effective at preventing scrub typhus because vectors of the pathogens tend to bite under clothing and they must pass over or under treated cloth before attachment. Further studies on use of treated clothing by civilians are needed, especially with respect to Lyme disease in the United States and Europe, where the use of treated clothing for this purpose is based more on hope than evidence. It seems unlikely that treated clothing will ever be an important tool for large populations exposed to malaria and dengue because of the difficulty of assuring that a large proportion of all clothing is treated; however, improvements would certainly be justified for a reduction in risk based on occupational or recreational exposure.

Area repellent systems, especially mosquito coils, are popular for relief from flying, biting insects, but the level of protection is much less than 100% and their effectiveness is dependent on air movement when outdoors. Another potential drawback is that all current systems depend on dispersal of a volatile or finely dispersed chemical, raising concerns about various inhalation hazards. The most widely used area repellent device, the burning mosquito coil, has never been properly tested for its effectiveness at preventing malaria (Lawrance & Croft, 2004). Further development and evaluation of area repellent systems is justified in spite of their limitations because the public continues to want such technology, suggesting that a truly effective system would make a big difference in public health.

Topical repellents offer much promise as important tools for prevention of infections from vector-borne pathogens. Under the best application conditions, current products often provide nearly 100% protection from flying insects and significant protection from ticks. Although there is a vigorous search for additional active ingredients, real advances for disease control are dependent on improvements in use. The widespread application of those improvements is highly dependent on acceptance of their efficacy by the public health community, which remains justifiably skeptical about topical repellents' place in vector control. The recent high-quality studies of topical repellents' use against malaria have shown that they can reduce transmission under at least some circumstances, especially in conjunction with what has become standard use of ITNs. Calculated effectiveness based on much more economical studies of bite protection and user acceptability might be a practical method for wider evaluation of topical repellents, with the caution that diversion to untreated members of a population is a real possibility (Moore *et al.*, 2007). Other potential negative aspects of widespread repellent use might be selection of species that are tolerant to the repellents (Klun *et al.*, 2004), development of resistance to repellents (Stanczyk *et al.*, 2010), or unexpected health impacts of long-term, consistent application. It is difficult to evaluate the practical danger from development of resistance or selection for species that are naturally more tolerant to topical repellents, as coverage is seldom high enough to constitute a strong selective mechanism. Safety of products evaluated by the U.S. Environmental Protection Agency, at least, is evaluated based on assumptions of continuous use, so that concerns over long-term use might not be as serious as assumed.

The authors think that the technical challenges for public health use continue to be ease of application, user acceptability and price, exactly as is the case for ITNs. Indications that active ingredients could be many-fold more effective than DEET and other current active ingredients based on interruption of mosquito receptor physiology (Jones *et al.*, 2011) raises the possibility of completely new kinds of products that might make topical repellents a much more important tool for disease control.

The authors offer the following opinion of the current relationship between disease prevention and insect repellents, based on the literature reviewed in this study and recent comprehensive summaries of bite protection. Broadly defined, repellents are products used by individuals to reduce the number of bites from haematophagous arthropods. If these products stopped all biting all of the time, there would be no question that they would be the complete solution for prevention of disease from vector-borne pathogens. Of course, repellents are not such universally effective tools because their effectiveness is not perfect and their use is dependent on many factors. Ironically, individual application is both the biggest appeal and the biggest limitation to repellent use. By contrast, an effective repellent places control of disease in the hands of the person who needs protection. However, individual application by millions of people inevitably results in variation in the quality of application and consequent impact on transmission of pathogens. Although it is true that a reduction in the number of bites cannot hurt, it is also true that limited prevention of bites may not have any impact at all on disease when the

entomological inoculation rate is even moderately high. To the extent that medical entomologists are responsible members of the public health community, and to the extent that entomological interventions are accepted by the medical community, we need to work towards evidence-based, intelligent application of current repellent tools and development of new ones that fill gaps in our armamentarium. Integrated disease control, rather than simply reducing the number of bites, requires careful testing of combinations of methods in order to assemble a series of partially effective measures into a single programme that reduces the health burden to an acceptable level. Implementation of a programme that depends on action by all individuals in a community is always going to be a challenge, but not a hopeless one. Societies have had success influencing populations to participate effectively to accomplish complicated objectives such as education and food safety. The same community participation to stimulate effective measures by each individual to prevent disease from vector-borne pathogens should also be possible.

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